Not Simply a Structural Problem: Psychological Determinants of Headache in Patients with Tumors of the Sellar Region

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ABSTRACT

Objective Headache in patients with tumors of the sellar region (TSR) has previously been attributed entirely to biomechanical causes. This study aimed to investigate the influence of psychological determinants for the occurrence of and disability due to headaches in patients with TSR.

Methods This was a cross-sectional single-center study with a logistic regression approach. Eighty-four patients (75 %) with pituitary adenomas and 28 with other TSR prior to first-time neurosurgery were investigated. One-hundred and twelve patients received standardized questionnaires on personality, headache characteristics, and disability due to headache. Fifty-nine patients additionally filled in questionnaires about coping with stress and pain catastrophizing. Separate logistic regression models were used to predict the risk of headache occurrence and disability due to headache by personality, stress coping, and pain catastrophizing.

Results Conscientiousness, neuroticism, and pain catastrophizing were significant predictors of headache occurrence. The amount of explained variance for both models predicting headache occurrence was comparable to that in primary headache. Neuroticism, pain catastrophizing, and humor as a coping strategy predicted disability due to headache with a high variance explanation of 20–40 %.

Conclusion For the first time, we report data supporting a strong psychological influence on headache and headache-related disability in patients with TSR, which argue against purely mechanistic explanatory models. Physicians treating patients with TSR and headaches should adopt an integrative diagnostic and treatment approach, taking the biopsychosocial model of pain into account.

Introduction

With a prevalence of 37 % to 70 % [1, 2], headache is one of the most frequent clinical symptoms associated with pituitary adenomas and other tumors of the sellar region (TSR) and frequently leads to their incidental discovery. So far, research on the underlying pathophysiological mechanisms has focused almost exclusively on bio-

logical explanations such as tumor size, invasiveness, high intrasellar pressure, hormonal oversecretion, and/or inflammatory processes [3]. However, none of the multiple biological factors investigated until now convincingly predict the occurrence of headache in patients with TSR or its improvement after surgery [3, 4]. Additionally, no unifactorial explanation is in line with the heterogeneous clinical picture of headache in patients with TSR, which varies considerably with regard to type, location, severity, frequency, and duration [4, 5].

Psychological factors are well-known strong predictors for the development of primary headaches. Personality traits, stress coping, and pain catastrophizing all influence the risk of headache occurrence and pain severity, and disability caused by headache [6–8]. The importance of these factors is acknowledged in the biopsychosocial model of pain [9], which is well established for the explanation of primary headaches. In stark contrast, clinical counseling and treatment of headaches in relation to the pituitary and other sellar pathologies are often influenced only by mechanistic pathophysiological explanations.

We previously reported that tumor-specific characteristics in patients with TSR, among them tumor size, cavernous sinus invasion, and hormonal oversecretion, did not relate to occurrence and disability due to headache, nor to their improvement after surgical tumor removal [4]. In line with a number of other studies, we concluded that a purely biomedical model of pain cannot suitably explain headache occurrence and headache-related disability in patients with TSR. For the present analysis, we, therefore, investigated three major psychological domains known to be crucial for the explanation of aspects of primary headache in the same, large patient group. We hypothesized that these factors, outlined below, would predict the risk of headache and headache-related disability in patients with pituitary adenomas and other TSR in a similar fashion as in primary headaches.

Personality

is a set of dispositions that defines a person's individuality and influences how a person acts, thinks, or feels. It comprises those psychological characteristics, both inherent and acquired, that seem central to a person and stay invariable over time and contexts [10]. It is best described and operationalized along five continuous dimensions, known as the "Big Five," including extraversion, neuroticism, conscientiousness, agreeableness, and openness to experience [11]. Especially neuroticism, with its core features of emotional instability, and an inclination towards negative feelings, has consistently been linked to primary headache in several studies [6, 12, 13].

Stress Coping

is the sum of all cognitive and behavioral efforts to manage stress [14]. Since stress is regarded as one of the most common triggers of headache attacks [15], the ability to cope with stressful events represents an important interindividual determinant of primary headache [7, 16, 17]. Although coping strategies are rarely universally adaptive or universally maladaptive, the prolonged and consistent use of some coping strategies can result in a loss of self-efficacy and poor health. While the effect of coping strategies on headache has not been investigated in patients with sellar masses, previous research has shown that patients treated for pituitary adenomas display different and less effective coping strategies compared with healthy controls [18] and that maladaptive coping strategies negatively affect the quality of life (QoL) in patients with pituitary adenomas such as in Cushing's disease [19].

Pain Catastrophizing

is defined as an exaggerated negative appraisal of perceived or anticipated pain. It is the tendency to magnify the significance of the perceived pain and to react with worry and fear [20]. Pain catastrophizing has been linked to a heightened pain experience and increased pain-related disability in a vast number of diseases, including rheumatoid arthritis and low-back pain [20]. In patients with primary headaches, pain catastrophizing is a strong predictor of pain intensity, the impact of headaches on daily living and disability due to headaches [8, 21]. It also affects the quality of life [22] and increases the risk for depression, anxiety, and low self-efficacy [23].

Materials and Methods

Study Procedure

This cross-sectional, single-center study was part of an extensive research project on headaches in patients with pituitary adenomas, and other TSR carried out at the Department of Neurosurgery of the University Hospital Erlangen. The Ethics Committee of the University of Erlangen-Nuremberg approved the study in July 2012 (Re.-No. 57_12 B, amendment February 2013). It was conducted according to the Declaration of Helsinki. All patients provided written informed consent.

Of 169 contacted patients, 112 patients scheduled for first-time surgery of TSR at the Department of Neurosurgery, University Hospital Erlangen, took part in the research project. Patients aged under 18 years or with a history of brain injury, known alcohol or substance abuse, acute psychotic illnesses, or insufficient German language fluency were excluded. Prior to surgery, all patients received questionnaires on headaches on a handheld computer (PainDetect, software version 4, provided by Pfizer GmbH, Germany) [24] exploring the presence, location, and type of headache as well as disability due to headache (Migraine Disability Assessment (MIDAS) and the Essen Headache Inventory (EHI).

For the present research question, psychological self-rating questionnaires, also distributed before neurosurgery, were analyzed in connection with the headache inventories. All investigated patients filled in a paper-pencil version of the personality inventory NEO-Five Factor Inventory (NEO-FFI) which was completed by all but two patients (110/112). The last consecutive 71 patients of the study group additionally received two further psychological inventories assessing coping and pain catastrophizing, namely the Brief-COPE and the Pain Catastrophizing Scale (PCS). Fifty-nine patients fully completed these additional questionnaires. Within the entire research project, we also collected data on histological and clinical diagnoses, tumor characteristics, and hormonal abnormalities, which are reported along with their relation to headache and headache-related disability in [4].

Study Sample

All patients included were scheduled for neurosurgical removal of a TSR. Their mean age was 51.5 ± 17.1 years (18.0–84.5 years). Fifty-three of the patients (47.3 %) were male, and 59 (52.7 %) were female. Eighty-four patients (75.0 %) were operated on for pituitary adenomas, and 28 patients (25 %) were operated on for other TSR. Fifty-nine of the patients (52.7 %) reported the occurrence of headache within the last three months before surgery; of these, 30 (50.8 %) experienced none or mild disability due to headache, and 29 (49.2 %) experienced moderate or severe disability. The average MIDAS Score was 34.41 (SD 54.4). The characteristics of the study sample are summarized in ▶ **Table 1**.

Used Inventories

The *MIDAS* questionnaire assesses patients' headache-related disabilities. The PainDetect version of the questionnaire used in this study starts with an entry question about the presence of headaches within the last three months. All other items are only presented if the presence of a headache is confirmed. The questionnaire consists of five items asking for the number of days patients experienced activity limitations due to headaches. From these items, a sum score is calculated. A MIDAS score < 5 signifies *minimal or infrequent disability* (MIDAS Grade I), 6–10 signifies *mild disability* (MIDAS Grade II), 11–20 signifies *moderate disability* (MIDAS Grade III), and > 21 signifies *severe disability* (MIDAS Grade IV). Unique to the PainDetect version is an illustrated presentation of "headzones," on which patients can report exact headache locations. The MIDAS questionnaire has been validated in two population-based samples in the USA and UK, showing a good test-retest reliability, as well as adequate internal consistency and construct validity [25].

The EHI [26] is a screening tool for migraine, tension-type headache (TTH), and trigeminal autonomic cephalgias (TACs) based on the International Classification of Headache Disorders-2 [27]. All items are only presented to the patients if they confirm in an entry question that they currently have a headache. The questionnaire has three modules, which assess the detailed diagnostic criteria of migraine, TTH, and TAC by yes/no-items. Additionally, the number of days per month when the headache was present at all and when pain medication was taken, is queried. The questionnaire was validated in 278 headache patients from a clinical population, demonstrating an adequate construct validity and a good test-retest reliability [26].

The *NEO-FFI* is a personality questionnaire that comprises 60 items measuring the "Big Five" scales (*extraversion*, *neuroticism*, *agreeableness*, *conscientiousness*, and *openness to experience*) on a 5-point Likert scale [28]. It is widely used and demonstrates excellent psychometric qualities in a non-clinical population with over 10,000 participants. Age and sex-specific norms from a German representative quota sample are available [29].

The *BriefCOPE* is a shorter version of the established COPE questionnaire [30]. It consists of 28 items measuring 14 different coping strategies: *self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion*, and *self-blame*. Responses are given on a 4-point Lik-

▶ **Table 1** Description of the study sample.

Variable	n	%
Histopathological diagnoses (n = 112)		
Pituitary adenoma	84	75
Craniopharyngeoma	2	2
Meningeoma	6	5
Rathke's cleft cyst	6	5
Colloid cyst	4	4
Normal pituitary tissue[a]	2	2
Other	8[b]	7
Clinical diagnoses (n = 85)		
Inactive pituitary adenoma	40	36
Prolactinoma	11	10
Cushing's disease	14	13
Acromegaly	16	14
Pituitary apoplexy	4	4
Adenoma Size (n = 84)		
Micro	18	21
Macro	66	79
Tumor location in the sellar region (n = 102)		
Middle	55	54
Side	47	46
Cavernous sinus invasion (n = 109)		
Yes	38	35
No	71	65
Optic chiasm compression (n = 111)		
Yes	40	36
No	71	64
Headache occurrence (n = 112)		
Within the last three month (MIDAS)	59	53
On the day of the study (EHI)	49	44
Headache type[c] (EHI; n = 45)		
Migraine without aura	21	47
Migraine with aura	12	27
Chronic daily headache	13	29
Tension type headache	12	27
Cluster headache	5	11
Medication induced headache	2	4
Not classifiable headache	8	18
Mixed headache types	16	36
Headache location (n = 49)		
Frontal	26	53
Holocranial	7	14
Occipital	3	6
Right side	2	4
Various locations	11	22

[a] Normal pituitary tissue in patients with a clinical diagnosis of central Cushing´s disease.; [b] Others are: epidermoid (n = 1), spindle-cell oncozytoma (n = 1), metastasis (n = 1), hypophysitis (n = 1), chordoma (n = 1), collagen connective tissue with ossification and calcification (n = 1), carcinoma (n = 1), metastasis of breast cancer (n = 1).; [c] Multiple answers were possible.

ert-Scale. Adequate validity of the German version has recently been shown in a heterogeneous non-clinical sample with over 600 participants [31].

The *PCS* measures catastrophizing thoughts and feelings concerning pain on 13 items. Answers are given on a 5-point Likert scale. The results are added up for a total score. Also, three subscales, namely *rumination*, *magnification*, and *helplessness,* can be calculated. An adequate validity of the PCS has been documented repeatedly, and percentiles from a clinical norm sample with ca. 850 participants are available for interpretation [32].

Statistical Analyses

To predict the probability of headache or headache-related disability by the psychological factors investigated here, a logistic regression analysis needs to be performed. To this means, data analysis was conducted in three steps. First, the statistical requirements for logistic regressions were checked. Then, all results from the psychological questionnaires, NEO-FFI, PCS, and BriefCOPE were correlated with the outcome variables (*occurrence of headache in the last three months* (yes vs. no; MIDAS) and *disability due to headache* (none/mild vs. moderate/severe; MIDAS) by means of the point-biserial correlation coefficient r_{pb}. In an exploratory approach, predictors were chosen for the subsequent logistic regression models if one of two conditions were met: 1) if they were significantly correlated to the outcome variables and 2) if they were expected to be determinants of headache based on a review of the literature. In the third step, step-wise logistic regression models were calculated. Cases with missing data in the questionnaire scores were excluded from the logistic regression. Separate regression models were calculated for the first part (N = 110) and the second part (N = 59) of the study to minimize the number of cases that had to be excluded. Nagelkerke R^2_{Max} is reported to evaluate the amount of variance explained by the model. It ranges from 0 to 1, and $R^2_{Max} = 1$ denotes perfect variance explanation. The percentage of correctly predicted cases, the results of the Wald test and Odds ratios (OR) are given to judge the effect size.

Results

Correlation Analyses

Headache occurrence before surgery was positively correlated to *pain catastrophizing* ($r_{pb} = 0.273$, $p = 0.032$; cf. ▶ **Table 2**) and the coping strategy *positive reframing* - a strategy referring to the effort to change one's perspective by looking for something good in any stressful situation - ($r_{pb} = 0.262$, $p = 0.028$) and negatively correlated to the coping strategy *substance use* ($r_{pb} = -0.250$, $p = 0.037$). None of the personality variables was related to *headache occurrence*.

Disability due to headache was positively correlated to *pain catastrophizing* ($r_{pb} = 0.433$, $p = 0.000$), the personality trait *neuroticism* ($r_{pb} = 0.368$, $p = 0.000$), the coping strategies *positive reframing* ($r_{pb} = 0.296$, $p = 0.013$), and *humor* ($r_{pb} = 0.390$, $p = 0.001$). *Substance use* was negatively correlated to *disability due to headache* ($r_{pb} = -0.242$, $p = 0.044$).

Regression Model for the Prediction of Headache and Headache-Related Disability by Personality Traits

All five personality traits queried by the NEO-FFI were entered into the logistic regression model for the prediction of *headache occurrence*-based on earlier published reports. The resulting two-step model (cf. ▶ **Table 4** in the supplement), performed with the inclusion criterion of $p \leq 0.10$, indicates that *conscientiousness* and *neuroticism* add on to predict the *occurrence of headache* ($X^2 = 6.356$, $p = 0.042$). Patients with higher values of conscientiousness and neuroticism in the NEO-FFI were more likely to develop a headache prior to pituitary surgery. However, the final model explained only a small amount of variance (Nagelkerke $R^2_{Max} = 0.075$). For the prediction of disability due to headache, *neuroticism* was entered into the logistic regression model due to its correlation with this variable. The other four personality variables were entered based on a review of earlier studies. The logistic regression resulted in a one-step model (cf. ▶ **Table 4** in the supplement) with *neuroticism* as the only relevant predictor variable ($X^2 = 16.226$, $p = 0.000$). According to the highly significant Wald test, the risk of experiencing moderate/severe disability due to headache is elevated in patients with TSR and high neuroticism ($X^2 = 12.626$, $p = 0.000$). The model explained a medium amount of variance (Nagelkerke $R^2_{Max} = 0.200$).

Regression Model for the Prediction of Headache and Headache-Related Disability by Stress Coping and Pain Catastrophizing

The entered predictor variables for the prediction of headache occurrence were *pain catastrophizing, substance use*, and *positive reframing* based on their significant correlation to *headache occurrence* and *denial, humor, behavioral disengagement*, and *self-blame* based on the literature review. The logistic regression model retained *pain catastrophizing* in a one-step model (cf. ▶ **Table 5** in the supplement) as the only relevant predictor ($X^2 = 4.083$, $p = 0.043$). By tendency, the probability of having a headache was increased by higher pain catastrophizing ($X^2 = 3.727$, $p = 0.054$). The model explained a small amount of variance (Nagelkerke $R^2_{Max} = 0.090$). For the prediction of disability due to headache, *pain catastrophizing, substance use*, *positive reframing*, and *humor* were selected as potential predictors due to their correlation to this variable. The selection of the variables *denial*, *behavioral disengagement*, and *self-blame* as predictors was based on the literature review. The logistic regression resulted in a two-step model (cf. ▶ **Table 5** in the supplement), indicating that *pain catastrophizing* and *humor* were significant predictors of *disability due to headache* ($X^2 = 19.052$, $p = 0.000$). Both variables contributed to the explanation with substantial effect sizes, implying that pain catastrophizing and humor as a coping strategy both considerably increase the probability of experiencing moderate/severe disability due to headaches. The model explained a satisfactory amount of variance (Nagelkerke $R^2_{Max} = 0.407$). ▶ **Fig. 1** and ▶ **Fig. 2** summarize the odds ratios for the predictor variables obtained from the four logistic regression models.

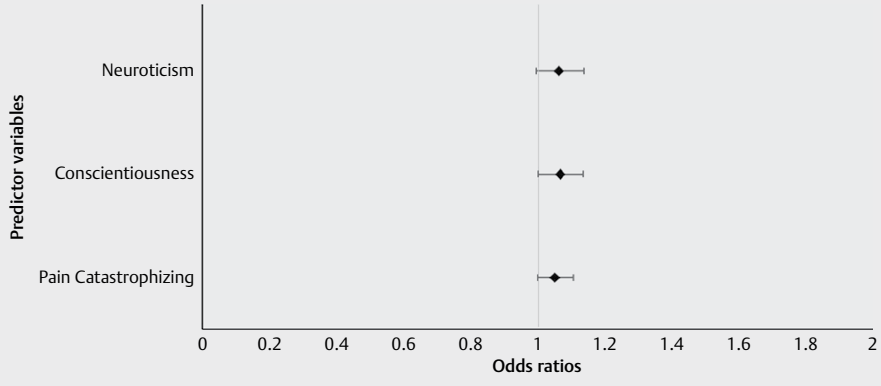
Discussion

While all previous studies focused on biological determinants of headache in patients with TSR, the present study is the first to demonstrate that psychological predictors play an important role in its explanation. The risk of headache occurrence was predicted by con-

▶ **Table 2** Point-biserial correlations between outcome variables and potential predictors from the NEO-FFI, BriefCOPE and PCS questionnaire.

	Headache occurrence			Disability due to headache		
	n	r_{pb}	p	n	r_{pb}	p
NEO-FFI N	110	0.138	0.150	110	0.368	0.000
NEO-FFI E	110	−0.020	0.839	110	−0.052	0.591
NEO-FFI O	110	−0.033	0.731	110	−0.089	0.353
NEO-FFI C	110	0.164	0.086	110	0.098	0.307
NEO-FFI A	110	−0.016	0.870	110	−0.039	0.686
PCS Total	62	0.273	0.032	62	0.433	0.000
BriefCOPE SD	70	0.176	0.146	70	0.157	0.193
BriefCOPE AC	69	0.201	0.097	69	0.085	0.487
BriefCOPE D	69	0.016	0.899	69	0.112	0.358
BriefCOPE SU	70	−0.250	0.037	70	−0.242	0.044
BriefCOPE ES	70	0.050	0.684	70	0.078	0.521
BriefCOPE IS	69	0.113	0.357	69	−0.170	0.162
BriefCOPE BD	68	−0.033	0.791	68	0.223	0.068
BriefCOPE V	69	−0.095	0.439	69	−0.040	0.743
BriefCOPE PR	70	0.262	0.028	70	0.296	0.013
BriefCOPE P	70	0.068	0.574	70	0.016	0.897
BriefCOPE H	70	0.157	0.195	70	0.390	0.001
BriefCOPE A	68	−0.039	0.751	68	−0.087	0.481
BriefCOPE R	69	0.067	0.586	69	0.088	0.472
BriefCOPE SB	70	0.074	0.544	70	0.231	0.055

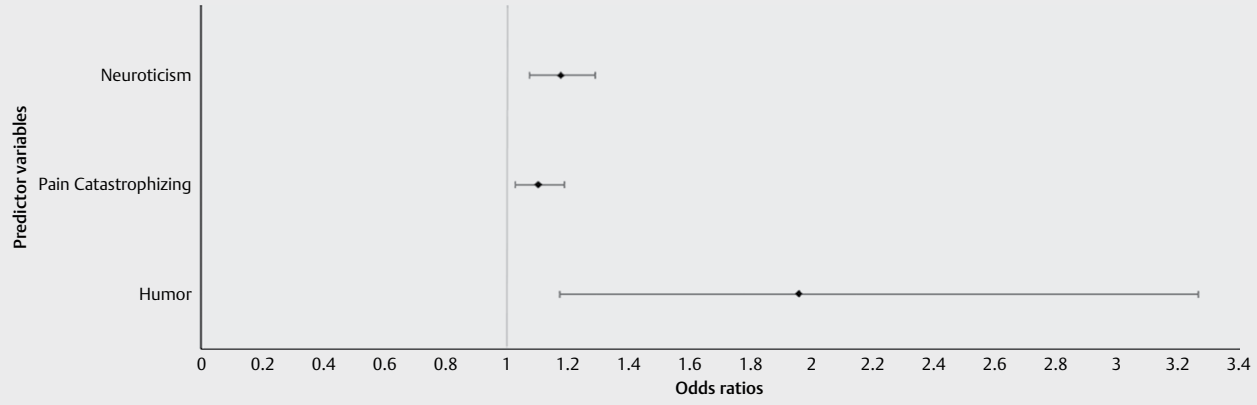
Note. NEO-FFI = Neo-Five Factor Inventory; N = neuroticism; E = extraversion; O = openness to experience; C = conscientiousness; A = agreeableness; PCS = Pain Catastrophizing Scale; SD = self-distraction; AC = active coping; D = denial; SU = substance use; ES = use of emotional support; IS = use of instrumental support; BD = behavioral disengagement; V = venting; PR = positive reframing; P = planning, H = humor; A = acceptance; R = religion; SB = self-blame.



▶ **Fig. 1** Predictors of headache occurrence.; Note. *The figure depicts odds ratios from the logistic regression models 1 and 3 for the prediction of headache occurrence and their 95 % confidence intervals. The odds ratio is the change in the odds of headache occurrence when the score of the questionnaire increases by one unit. Odds ratios > 1 reflect an increase in the odds, odds ratios < 1 reflect a decrease in the odds of headache occurrence.*

scientiousness, neuroticism, and pain catastrophizing. The amount of variance explained was comparable to that of similar models in studies on primary headaches [13, 33]. The effect of psychological factors on disability caused by headaches in patients with TSR was even more pronounced. In our study, pain catastrophizing and humor as a coping strategy alone explained around 40 % of the variance in headache-related disability, whereas neuroticism explained 20 % of the variance. This is of particular importance because disability due to headache was found entirely unrelated to biological factors in the same patient sample [4].

The impact of psychological factors on headaches in patients with TSR has so far not received much attention in research and clinical practice, even though a recent review article highlighted the absence of any convincing physiological explanation for headaches in patients with pituitary disease and underscored the challenges of attribution [5]. Yet, only one study investigated influenc-



▶ **Fig. 2** Predictors of disability due to headache.; Note. *The figure depicts odds ratios from the logistic regression models 2 and 4 for the prediction of disability due to headache and their 95 % confidence intervals. The odds ratio is the change in the odds of disability due to headache when the score of the questionnaire increases by one unit. Odds ratios > 1 reflect an increase in the odds, odds ratios < 1 reflect a decrease in the odds of disability due to headache.*

ing factors beyond biomedical determinants and found that a positive family history of headaches was more important than tumor size for explaining headaches in pituitary adenoma patients [2].

In this line, our data suggest that the understanding of headache in patients with TSR could be improved if it was no longer understood as a mere consequence of the mechanical and biochemical properties of the tumor, but as a complex interaction of multiple factors, including biological and psychological determinants. For years, the research on pain in general, and headache in particular, has been characterized by an integrative, biopsychosocial understanding and has found evidence for the importance of psychological factors across a multitude of diseases [9]. Such a perspective would open up new avenues of diagnosis and treatment of patients with headaches and TSR as well.

Our results indicate that psychological risk factors for headaches need to be assessed in the clinical endocrinological routine. Especially, the high impact of pain catastrophizing on disability caused by headaches observed in our patients is of particular relevance for the diagnostic and therapeutic decision-making process. Pain catastrophizing patients are more likely to use health care resources than other patients [20] and elicit increased offers of assistance by intense expression of pain [34]. Such pain behavior can result in a higher level of instrumental support and, thus, serve in the short term as a selectively adaptive coping strategy. On the other hand, it is also likely to lead to more extensive diagnostic measures and more invasive therapies, which are not always warranted. The possibility of primary headache disorders or other unrelated causes of headache should also be taken into account in patients with TSR unless a clear temporal and pathophysiological connection between the lesion and headache can be established, as is the case with pituitary apoplexy [35].

While our data suggest that patients with pituitary adenomas and other TSR are likely to benefit from considering psychological risk factors in headache and their appropriate treatment, there is, as yet, no interdisciplinary treatment concept involving medical, physical, and psychosocial interventions for them. While the short course of a doctor's visit will usually not allow for a detailed psychological assessment, empathetic attention to psychological topics, short screening questions, and a willingness to liaison with a psychotherapist, if necessary, could already be of considerable help. Moreover, for many headache types, non-pharmacological interventions like information, reassurance, relaxation training, physiotherapy, and aerobic exercise are easily accessible therapeutic options [36, 37]. In more serious cases, established pharmacological and multimodal treatment approaches for patients with primary headache [38] might work equally well for patients with headaches and TSR. ▶ **Table 3** gives a suggestion for the clinical management of these patients.

A strength of the present study is that it was conducted on a large data set which afforded us the opportunity for a detailed statistical analysis. Our analysis took into account three major psychological domains and led to models that account for a significant amount of variance in headache in patients with TSR. Still, the correlational nature of the study must be considered. Furthermore, the strong impact of humor as a coping strategy was unexpected. In this respect, we hypothesize that an injurious humor style such as self-defeating or aggressive humor was used by patients in our study group and caused the negative effect. The exact way different coping strategies, especially humor, influence headaches in patients with TSR cannot be fully explained by the results of the Brief-Cope, which was used as a screening tool for coping strategies in this explorative study. Future investigations should assess the role of humor in detail with more specific questionnaires.

In conclusion, the present study argues for better integration of psychological and biological aspects of headache in the clinical management of patients with TSR. Future research should broaden its focus from regarding tumor characteristics alone to determining the psychological contribution to headache in patients with TSR in more detail and drive forward the development and validation of multimodal treatment options.

▶ **Table 3** Suggestions for the management of patients with tumors of the sellar region and headache.

Take a headache history	Chronic (> 15 days/month) or acute headache?
	Headache onset in relation to diagnosis of pituitary disease?
	Headache location?
	Frequency and duration of headache attacks?
	Precipitating factors (e. g., stress, exertion, food intake)?
	Associated symptoms (e. g., nausea, photophobia, rhinorrhea)?
	Headache severity and effect on work and private life?
	Potential comorbidities (e. g., hypertension, depression, insomnia)?
	Psychological risk factors (e. g., pain catastrophizing, maladaptive coping strategies, negative stressors)?
	Medication intake?
Screen for pituitary apoplexy	Severe, sudden onset thunderclap headache often accompanied by ▪ visual disturbances and/or diplopia (esp. IIIrd cranial nerve palsy) ▪ deterioration of consciousness ▪ nausea and vomiting ▪ hypotension ▪ electrolyte disturbances, especially hyponatremia
Screen for other red flags[a]	Fever
	Meningism
	Deterioration of consciousness
	Rhinoliquorrea
	Focal neurological deficits
	Epileptic seizures
	Papilledema and deterioration of vision
Counsel the patient	Explain the possibility of primary headache disorders or other causes of headache unrelated to TSR
	Raise realistic expectations concerning pain reduction through neurosurgery
	Inform about non-invasive treatment options for headache
	Explain the role of psychological risk factors and encourage self-management (e. g., headache diary)
Explain treatment options[b]	Adjustment of lifestyle factors (e. g., sleep, exercise, caffeine reduction)
	Stress management techniques (e. g., relaxation, pacing activities, coping strategies)
	Acute or prophylactic pain medication
	In case of red flags →instant neurological or neurosurgical referral
	In case of chronic headache or noticeable psychological strain →consider psychotherapy or multimodal pain treatment
	Headache alone is rarely an indication for neurosurgery of sellar tumors

[a] Please note that this does not constitute a complete list of headache-related red flags, but those of special relevance in connection to the neurosurgical treatment of TSR; [b] for a comprehensive guideline on headache treatment options, refer, e. g., to Becker, 2015 [39].

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Conflict of interest/Competing interests

The authors declare no conflict of interest with respect to the research reported in this study.

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